ACP American College of Physicians®
Leading Internal Medicine, Improving Lives

CLINICAL GUIDELINE

Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Michael J. Barry, MD; Linda L. Humphrey, MD, MPH; and Mary Ann Forciea, MD; for the Clinical Guidelines Committee of the American College of Physicians*

Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on oral pharmacologic treatment of type 2 diabetes in adults. This guideline serves as an update to the 2012 ACP guideline on the same topic. This guideline is endorsed by the American Academy of Family Physicians.

Methods: This guideline is based on a systematic review of randomized, controlled trials and observational studies published through December 2015 on the comparative effectiveness of oral medications for type 2 diabetes. Evaluated interventions included metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium–glucose cotransporter-2 (SGLT-2) inhibitors. Study quality was assessed, data were extracted, and results were summarized qualitatively on the basis of the totality of evidence identified by using several databases. Evaluated outcomes included intermediate outcomes of hemoglobin A_{1c}, weight, systolic blood pressure, and heart rate; all-cause mortality; cardiovascular and cerebrovascular morbidity and mortality; retinopathy, nephropathy, and neuropathy; and harms. This guideline grades the recommendations by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.

Target Audience and Patient Population: The target audience for this guideline includes all clinicians, and the target patient population includes adults with type 2 diabetes.

Recommendation 1: *ACP recommends that clinicians prescribe metformin to patients with type 2 diabetes when pharmacologic therapy is needed to improve glycemic control. (Grade: strong recommendation; moderate-quality evidence)*

Recommendation 2: *ACP recommends that clinicians consider adding either a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin to improve glycemic control when a second oral therapy is considered. (Grade: weak recommendation; moderate-quality evidence.) ACP recommends that clinicians and patients select among medications after discussing benefits, adverse effects, and costs.*

Ann Intern Med. 2017;166:279-290. doi:10.7326/M16-1860 **Annals.org**
For author affiliations, see end of text.
This article was published at Annals.org on 3 January 2017.

Diabetes mellitus is the seventh leading cause of death in the United States. It also is a leading cause of morbidity, resulting in both microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (coronary artery, cerebrovascular, and peripheral vascular disease) complications. Type 2 diabetes mellitus is the most common form of the disease (affecting 90% to 95% of persons with diabetes), with a prevalence of approximately 29.1 million people in the United States (1). The risk for type 2 diabetes increases with age, and nearly 26% of people in the United States older than 65 years have diabetes (1). In addition, because of the rising obesity rate in the United States, the incidence and prevalence of diabetes mellitus are increasing substantially (2). The total direct and indirect costs associated with diabetes in the United States alone reached $245 billion in 2012 (1).

Management of type 2 diabetes often includes lifestyle modification and pharmacologic therapy. In the United States, several unique classes of drugs are approved by the U.S. Food and Drug Administration (FDA) to treat hyperglycemia in type 2 diabetes, all of which vary regarding cost and harms. Most adults diagnosed with type 2 diabetes receive treatment with oral medications only rather than injection medications, such as insulin or glucagon-like peptide-1 (GLP-1) receptor agonists (3).

Guideline Focus and Target Population

Since the publication of the 2012 American College of Physicians (ACP) guideline on the comparative effectiveness and safety of oral medications for the treatment of type 2 diabetes, several new studies evaluated medications for this disease, and the FDA ap-

See also:

Editorial comment 309
Summary for Patients I-18

Web-Only
CME quiz

* This paper, authored by Amir Qaseem, MD, PhD, MHA; Michael J. Barry, MD; Linda L. Humphrey, MD, MPH; and Mary Ann Forciea, MD, was developed for the Clinical Guidelines Committee of the American College of Physicians. Individuals who served on the Clinical Guidelines Committee from initiation of the project until its approval were Mary Ann Forciea, MD† (*Chair*); Nick Fitterman, MD (*Vice Chair*)†; Michael J. Barry, MD†; Cynthia Boyd, MD, MPH‡; Carrie Horwitch, MD, MPH†; Linda L. Humphrey, MD, MPH†; Alfonso Iorio, MD, PhD‡; Devan Kansagara, MD, MCR†; Scott Manaker, MD, PhD‡; Robert M. McLean, MD†; Sandeep Vijan, MD, MS‡; and Timothy J. Wilt, MD, MPH†. Approved by the ACP Board of Regents on 16 July 2016.
† Author (participated in discussion and voting).
‡ Nonauthor contributor (participated in discussion but excluded from voting).

proved several new agents. New information in the updated review includes evidence on the FDA-approved sodium–glucose cotransporter-2 (SGLT-2) inhibitor class of drugs and on additional dipeptidyl peptidase-4 (DPP-4) inhibitors, as well as further evidence on other drugs included in the 2011 review. The purpose of this ACP guideline is to present the updated evidence regarding the oral pharmacologic treatment of type 2 diabetes; it replaces the 2012 ACP guideline on the same topic (4). The target audience for this guideline includes all clinicians, and the target patient population includes all adults with type 2 diabetes. These recommendations are based on a systematic evidence review sponsored by the Agency for Healthcare Research and Quality (AHRQ) (5) as well as a recently published update of the review (6). Although the focus of this guideline is oral pharmacologic therapy, lifestyle modifications are an important management strategy for type 2 diabetes. Injectable medications, including insulin, also are important treatments, although most patients prefer oral agents as initial therapy. This guideline is endorsed by the American Academy of Family Physicians.

METHODS

Systematic Review of the Evidence

The evidence review was conducted by the AHRQ Johns Hopkins Evidence-based Practice Center. Additional methodological details can be found in the Appendix (available at Annals.org), the full report (5), and the published article (6). Reviewers searched several databases for studies published in English from April 2009 through March 2015. An updated search through December 2015 found evidence that changed from low or insufficient quality to high or moderate quality. Reviewers combined data when possible by using meta-analysis and assessed risk of bias and study quality according to established methodology. The study population included adults (aged ≥18 years) with type 2 diabetes.

The review evaluated head-to-head comparisons of oral monotherapy with metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, and SGLT-2 inhibitors; comparisons of metformin monotherapy with a metformin-based combination; and comparisons of metformin-based combinations in which the second medication was one of the monotherapies described earlier. The review contains additional information on injectables, including GLP-1 receptor agonists and insulin, which is not considered in the guideline. Evaluated outcomes included intermediate outcomes of hemoglobin A_{1c} (HbA_{1c}) levels, weight, systolic blood pressure (for SGLT-2 inhibitors only), and heart rate (for SGLT-2 inhibitors only); all-cause mortality; cardiovascular and cerebrovascular morbidity and mortality; retinopathy, nephropathy, and neuropathy; and harms.

Table 1. The American College of Physicians' Guideline Grading System*

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

* Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) workgroup.

Grading the Evidence and Developing Recommendations

This guideline was developed by the ACP Clinical Guidelines Committee (CGC) according to ACP's guideline development process, details of which can be found in the methods paper (7). This guideline rates the evidence and recommendations by using ACP's guideline grading system (Table 1).

Peer Review

The AHRQ evidence review was sent to invited peer reviewers and posted on the AHRQ Web site for public comments, and the published review article was peer reviewed through the journal. The guideline was peer reviewed through the journal and posted online for comments from ACP Regents and Governors, who represent physician members at the regional level.

COMPARATIVE BENEFITS OF ORAL MEDICATIONS FOR TYPE 2 DIABETES

Long-Term All-Cause Mortality, Microvascular, and Macrovascular Outcomes

Evidence from new studies (52 randomized, controlled trials and 13 observational studies, mostly 1 year or less in duration) was either low quality or insufficient for evaluating clinical outcomes, such as mortality, cardiovascular mortality and morbidity, retinopathy, nephropathy, and neuropathy.

All-Cause Mortality

Low-quality evidence comparing metformin monotherapy with sulfonylurea monotherapy showed that metformin was associated with lower all-cause mortality; however, results were inconsistent across studies (8–16). Generally, if low-quality evidence was available for all-cause mortality, it showed no difference between monotherapies and combination therapies.

Cardiovascular Mortality

The review found moderate-quality evidence that metformin was associated with lower cardiovascular mortality (≥2 years) than sulfonylureas, on the basis of 2 randomized, controlled trials (8, 9) and 3 nonexperimental studies (10, 11, 17). The CGC reviewed the individual studies and found the 2 trials to be underpowered, with no significant reductions in cardiovascular mortality with metformin versus sulfonylureas, and therefore considered the quality of evidence to be low.

The committee also noted that in 2 of the nonexperimental studies, the combination of metformin and a sulfonylurea significantly reduced overall (9) and cardiovascular (16) mortality compared with a sulfonylurea alone.

Evidence for all other comparisons was insufficient or low quality.

Cardiovascular and Cerebrovascular Morbidity

Low-quality evidence showed that metformin monotherapy was associated with lower cardiovascular morbidity than sulfonylurea monotherapy, although results were inconsistent across studies (8–16). Evidence for all other comparisons was insufficient or low quality, thus inconclusive for this outcome.

Retinopathy, Nephropathy, and Neuropathy

All randomized, controlled trials were short term, and evidence for all comparisons was insufficient or low quality, thus inconclusive for these outcomes.

Intermediate Outcomes

HbA_{1c} Levels

Monotherapy Versus Monotherapy. As in the 2012 guideline, most diabetes medications had similar efficacy in reducing HbA_{1c} levels. High-quality evidence from the 2011 review showed no difference between metformin and sulfonylureas regarding their effect on HbA_{1c} levels (hence, evidence was not updated) (18). High-quality evidence also showed no difference between metformin and thiazolidinediones (19–41) or between thiazolidinediones and sulfonylureas in reducing HbA_{1c} levels (32, 35, 40–52). High-quality evidence showed that metformin reduced HbA_{1c} levels to a greater extent than DPP-4 inhibitors (mean between-group difference, −0.43% [CI, −0.55% to −0.31%]) (37, 53–60), and moderate-quality evidence favored sulfonylureas over DPP-4 inhibitors (mean between-group difference, −0.21% [CI, −0.32% to −0.09%]) (61–63). Low-quality evidence showed no difference between metformin and SGLT-2 inhibitors (64–66).

Monotherapy Versus Combination Therapy. High-quality evidence showed that all combination therapies that included metformin were superior to metformin monotherapy in reducing HbA_{1c} levels (thiazolidinediones: pooled between-group difference in HbA_{1c} for baseline HbA_{1c} >8%, 0.88% [CI, 0.73% to 1.04%], and for baseline HbA1c <8%, 0.43% [CI, 0.23% to 0.63%]; sulfonylureas: 0.94% [CI, 0.68% to 1.19%]; DPP-4 inhibitors: 0.65% [CI, 0.60% to 0.70%]; SGLT-2 inhibitors: 0.61% [CI, 0.52% to 0.71%]) (5, 6).

Combination Therapy Versus Combination Therapy. Moderate-quality evidence showed that the combination of metformin plus an SGLT-2 inhibitor was superior to metformin plus a DPP-4 inhibitor (pooled between-group difference in HbA_{1c}, 0.17% [CI, 0.08% to 0.26%]) (67–70) and to metformin plus a sulfonylurea (pooled between-group difference in HbA_{1c}, 0.17% [CI, 0.10% to 0.20%]) (71–75). Moderate-quality evidence showed that metformin plus a thiazolidinedione was superior to metformin plus a DPP-4 inhibitor (pooled between-group difference in HbA_{1c}, −0.12% [CI, −0.21% to −0.02%]) (63, 76–79). Moderate-quality evidence showed no difference between metformin plus a thiazolidinedione and metformin plus a sulfonylurea (80–87). Moderate-quality evidence also showed no substantial differences regarding most other comparisons.

Weight

Monotherapy Versus Monotherapy. According to high-quality evidence from the 2011 review, metformin reduced weight more than thiazolidinediones (pooled mean between-group difference, −2.6 kg [CI, −4.1 to −1.2 kg]) or sulfonylureas (pooled mean between-group difference, −2.7 kg [CI, −3.5 to −1.9 kg]) (hence, evidence was not updated) (18). High-quality evidence also showed that metformin was more favorable than DPP-4 inhibitors for weight reduction (pooled mean between-group difference, −1.3 kg [CI, −1.6 to −1.0 kg]) (37, 53–60). Moderate-quality evidence showed that SGLT-2 inhibitors reduced weight more than metformin (range of between-group differences, −1.3 to −1.4 kg) (64, 66) or DPP-4 inhibitors (between-group difference, −2.5 to −2.7 kg) (88) and that DPP-4 inhibitors reduced weight more than thiazolidinediones (range of between-group differences, −2.3 to −2.5 kg) (37, 89). High-quality evidence showed that sulfonylureas caused less weight gain than thiazolidinediones (pooled mean between-group difference, 1.2 kg [CI, 0.6 to 1.8 kg]) (35, 41, 43, 44, 50, 52, 90). Moderate-quality evidence indicated that DPP-4 inhibitors were favored over sulfonylureas (range of between-group differences, 0.7 to 1.8 kg) (61–63).

Monotherapy Versus Combination Therapy. High-quality evidence showed that metformin monotherapy reduced weight more than metformin plus a thiazolidinedione (pooled between-group difference, −2.2 kg [CI, −2.6 to −1.9 kg]) (26, 36, 63, 91–93) or metformin plus a sulfonylurea (pooled between-group difference, −2.2 kg [CI, −3.4 to −1.0 kg]) (94–103). High-quality evidence showed no difference in mean weight between metformin monotherapy and metformin plus a DPP-4 inhibitor (53, 56, 57, 59, 63, 67, 69, 103–115). Metformin plus an SGLT-2 inhibitor was superior to metformin monotherapy for weight reduction (high-quality evidence; pooled between-group difference, 2.0 kg [CI, 1.5 to 2.5 kg]) (64, 67, 69, 116, 117).

Combination Therapy Versus Combination Therapy. The combination of metformin plus a DPP-4 inhibitor was superior for weight reduction compared with metformin plus a thiazolidinedione (moderate-quality evidence; pooled mean between-group difference, 2.7 kg [CI, 0.8 to 4.5 kg]) (63, 76–78) and compared with metformin plus a sulfonylurea (high-quality evidence; pooled mean between-group difference, 2.2 kg [CI, 1.8 to 2.5 kg]) (103, 118–121). High-quality evidence showed that the combination of metformin plus an SGLT-2 inhibitor was superior to metformin plus a sulfonylurea (pooled mean between-group difference, 4.7 kg [CI, 4.4 to 5.0 kg]) (72–74).

Systolic Blood Pressure and Heart Rate

Monotherapy Versus Monotherapy. Moderate-quality evidence showed that SGLT-2 inhibitors reduced systolic blood pressure more than metformin (pooled between-group difference, 2.8 mm Hg [CI, 2.6 to 3.0 mm Hg]) (64, 65). The evidence was insufficient to draw conclusions regarding the effects on heart rate of any monotherapy comparisons.

Monotherapy Versus Combination Therapy. High-quality evidence showed that metformin plus an SGLT-2 inhibitor reduced systolic blood pressure more than metformin alone (pooled between-group difference, 4.4 mm Hg [CI, 2.9 to 6.0 mm Hg]) (64, 67–69, 111, 116, 117, 122–124).

The evidence was insufficient to draw conclusions regarding the effects on heart rate of any metformin combination therapy compared with metformin alone.

Combination Therapy Versus Combination Therapy. The combination of metformin and an SGLT-2 inhibitor reduced systolic blood pressure more than that of metformin and a sulfonylurea (high-quality evidence; pooled between-group difference, 5.1 mm Hg [CI, 4.2 to 6.0 mm Hg]) (74, 75, 114) or metformin and a DPP-4 inhibitor (moderate-quality evidence; pooled between-group difference, 4.1 mm Hg [CI, 3.6 to 4.6 mm Hg]) (67–70).

Moderate-quality evidence indicated that the combination of metformin and an SGLT-2 inhibitor increased heart rate less than metformin plus a sulfonylurea (pooled between-group difference, 1.5 beats/min [CI, 0.6 to 2.3 beats/min]) (72–74).

Comparative Harms of Oral Medications for Type 2 Diabetes

Hypoglycemia

Moderate-quality evidence showed that metformin monotherapy was associated with a lower risk for mild, moderate, or total hypoglycemia than metformin plus a sulfonylurea (94, 95, 97, 101–103, 125–128). Moderate-quality evidence also showed that monotherapy with either metformin (37) or a thiazolidinedione (9, 43) was associated with a lower risk for severe hypoglycemia than sulfonylureas. Moderate-quality evidence also showed that monotherapy with a DPP-4 inhibitor (61–63, 129) was associated with a lower risk for mild, moderate, or total hypoglycemia than sulfonylureas.

The combination of metformin and a DPP-4 inhibitor was associated with a lower risk for severe hypoglycemia than metformin plus a sulfonylurea (high-quality evidence) (118–120, 130–133). Moderate-quality evidence showed that metformin plus an SGLT-2 inhibitor was associated with a lower risk for severe hypoglycemia than metformin plus a sulfonylurea (74, 75, 114).

Gastrointestinal Side Effects

High-quality evidence showed no difference between thiazolidinediones and sulfonylureas for gastrointestinal side effects (9, 41, 43, 44, 134). Moderate-quality evidence indicated no difference between metformin plus a thiazolidinedione and metformin plus a sulfonylurea (82–85, 87).

Genital Mycotic Infections

The SGLT-2 inhibitors, used alone or combined with metformin, increased the risk for genital mycotic infections compared with all other monotherapies or combination therapies. Metformin was associated with fewer genital mycotic infections than SGLT-2 inhibitors (moderate-quality evidence) (64, 65).

High-quality evidence showed that metformin monotherapy was associated with a lower risk for genital mycotic infections than metformin plus an SGLT-2 inhibitor (64, 67, 68, 116, 117, 122, 135, 136). The combination of metformin and a DPP-4 inhibitor was associated with a lower risk for genital mycotic infections than metformin plus an SGLT-2 inhibitor (moderate-quality evidence) (66–70). High-quality evidence showed that metformin plus a sulfonylurea was associated with a lower risk for genital mycotic infections than metformin plus an SGLT-2 inhibitor (71, 74, 75, 114).

Multiple Chronic Conditions

Patients with multiple chronic conditions often were excluded from the studies included in the systematic review.

Summary

Although all oral diabetes medications reduced HbA_{1c} levels, the DPP-4 inhibitors were inferior to metformin and sulfonylureas for this outcome. Metformin had a greater benefit on weight than all agents except the SGLT-2 inhibitors, and SGLT-2 inhibitors were more effective than metformin in reducing blood pressure. Combination therapies with metformin and an SGLT-2 or a DPP-4 inhibitor were superior to metformin alone in reducing HbA_{1c} levels, weight, and blood pressure. Head-to-head comparisons of various combination therapies showed that metformin plus an SGLT-2 inhibitor was superior to metformin plus a DPP-4 inhibitor or metformin plus a sulfonylurea in reducing HbA_{1c} levels, although the CGC felt that these differences were of dubious clinical importance. Metformin monotherapy was associated with a low risk for hypoglycemia compared with other monotherapies. Evidence showed that sulfonylureas increased the risk for hypoglycemia, thiazolidinediones for congestive heart failure, and SGLT-2 inhibitors for genital mycotic infections. Thiazolidinediones and sulfonylureas were associated with weight gain when compared with metformin, DPP-4 inhibitors, and SGLT-2 inhibitors.

The CGC generally agreed with the evidence review that all evidence from comparisons of monotherapies and combination therapies with respect to overall and cardiovascular mortality, as well as cardiovascular morbidity, was of low quality. However, the committee felt that the evidence showing greater cardiovascular mortality with sulfonylureas than metformin mono-

Figure. Summary of the American College of Physicians guideline on oral medications for type 2 diabetes.

ACP[SM]
American College of Physicians
Leading Internal Medicine, Improving Lives

Summary of the American College of Physicians Guideline on Oral Medications for Type 2 Diabetes

Disease/Condition	Type 2 diabetes
Target Audience	Internists, family physicians, other clinicians
Target Patient Population	Adults with type 2 diabetes
Interventions Evaluated	Oral pharmacologic treatments: metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors
Outcomes Evaluated	Clinical outcomes: all-cause mortality, cardiovascular and cerebrovascular morbidity and mortality, retinopathy, nephropathy, neuropathy Intermediate outcomes: HbA_{1c}; weight; systolic blood pressure; harms: hypoglycemia, gastrointestinal side effects, genital mycotic infections
Benefits	Clinical Outcomes Metformin monotherapy was associated with a lower risk for cardiovascular mortality than sulfonylurea monotherapy. HbA_{1c} Most drugs reduced HbA_{1c} to similar levels. DPP-4 inhibitors reduced HbA_{1c} levels less than metformin or sulfonylureas. All combination therapies with metformin were superior to metformin monotherapy. Weight Metformin was better than thiazolidinediones, sulfonylureas, or DPP-4 inhibitors for weight. Combinations of metformin and SGLT-2 inhibitor agonists reduced weight more than metformin monotherapy. Thiazolidinediones and sulfonylureas, either alone or in combination therapy, were associated with worse weight outcomes. Systolic Blood Pressure SGLT-2 inhibitors, as monotherapy or combined with metformin, reduced systolic blood pressure compared with metformin monotherapy.
Harms	Metformin: increased risk for gastrointestinal side effects Sulfonylureas: increased risk for hypoglycemia compared with other drugs Thiazolidinediones: increased risk for heart failure SGLT-2 inhibitors: increased genital mycotic infections
Recommendations	***Recommendation 1: ACP recommends that clinicians prescribe metformin to patients with type 2 diabetes when pharmacologic therapy is needed to improve glycemic control. (Grade: strong recommendation; moderate-quality evidence)*** ***Recommendation 2: ACP recommends that clinicians consider adding a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin to improve glycemic control when a second oral therapy is considered. (Grade: weak recommendation; moderate-quality evidence.) ACP recommends that clinicians and patients select among medications after discussing benefits, adverse effects, and costs.***
Clinical Considerations	Nonpharmacologic therapy includes dietary modifications, regular exercise, lifestyle modifications, and weight loss. Management of type 2 diabetes often involves pharmacologic and nonpharmacologic therapies and includes patient education, evaluation, patient self-management for microvascular and macrovascular complications, treatment of hyperglycemia, and minimization of cardiovascular and other long-term risk factors. Initiation of pharmacologic therapy is an important approach for the effective management of type 2 diabetes when weight loss or lifestyle modification fails. Metformin monotherapy effectively decreases glycemic levels when used in monotherapy and combination therapy with a second agent. Metformin also reduces body weight. Although combination therapy reduces HbA_{1c} levels more effectively than monotherapy, it is associated with more adverse events. The DPP-4 inhibitors saxagliptin and alogliptin may increase the risk for heart failure, especially in patients who already have heart or kidney disease. Metformin is considered safe for patients with mild chronic kidney disease and some patients with moderate kidney impairment (but is contraindicated in those with an estimated glomerular filtration rate <30 mL/min/1.73 m^2).

DPP-4 = dipeptidyl peptidase-4; HbA_{1c} = hemoglobin A_{1c}; SGLT-2 = sodium–glucose cotransporter-2.

Table 2. Comparative Efficacy, Adverse Effects, and Costs for Add-on Oral Therapies to Metformin

Comparative Efficacy vs. Other Combinations With Metformin (Quality of Evidence)	Comparative Harms vs. Other Combinations With Metformin/Class Adverse Effects and FDA Warnings	Agents	Fair Price for a 60-d Supply, $*	Adverse Effects
SUs				
SU + metformin favored for weight vs. TZD + metformin (moderate)	Higher risk for hypoglycemia than with metformin combinations with TZD, DPP-4 inhibitor, or SGLT-2 inhibitor	Glipizide, 5 mg	9	Diarrhea, gas, jitteriness, dizziness, uncontrollable shaking, red or itchy skin, rash, hives, and blisters
		Glimepiride, 4 mg	14	Dizziness and nausea
		Glyburide (DiaBeta, Sanofi-Aventis), 5 mg	111	Nausea and upper abdominal fullness
		Glyburide (Glynase, Pfizer), 6 mg	226	Nausea and upper abdominal fullness
TZDs				
TZD + metformin favored for short-term CVD mortality (rosiglitazone only) (low) and HbA_{1c} vs. DPP-4 inhibitor + metformin (moderate)	TZDs increase risk for congestive heart failure May also be associated with increased risk for fracture or bladder cancer	Pioglitazone, 30 mg	24	Headache; muscle, arm, or leg pain; sore throat; and gas
		Rosiglitazone (Avandia, GlaxoSmithKline), 2 mg	178	Headache, runny nose and other cold symptoms, sore throat, and back pain
DPP-4 inhibitors				
DPP-4 inhibitor + metformin favored for long-term all-cause mortality, long-term CVD mortality, and CVD morbidity vs. SU + metformin (low) DPP-4 inhibitor + metformin favored for short-term CVD morbidity vs. pioglitazone + metformin (low) DPP-4 inhibitor + metformin favored for weight vs. SU + metformin (high) or TZD + metformin (moderate)	FDA warns that sitagliptin, saxagliptin, linagliptin, and alogliptin may be associated with potentially severe and disabling joint pain	Alogliptin, 25 mg	335	Headache, stuffy or runny nose, sore throat, and joint pain
		Linagliptin (Tradjenta, Boehringer Ingelheim), 5 mg	734	Headache and joint pain
		Saxagliptin (Onglyza, AstraZeneca), 5 mg	752	Sore throat, headache, and joint pain
		Sitagliptin (Januvia, Merck), 100 mg	746	Stuffed or runny nose, sore throat, headache, diarrhea, nausea, and joint pain
SGLT-2 inhibitors				
SGLT-2 inhibitor + metformin favored for CVD mortality (low), HbA_{1c} (moderate), weight (high), systolic blood pressure (high), and heart rate (moderate) vs. SU + metformin SGLT-2 inhibitor + metformin favored for weight and systolic blood pressure (moderate) vs. DPP-4 inhibitor + metformin	Higher risk for genital mycotic infection than metformin alone or metformin combinations with SU or DPP-4 inhibitor FDA warns that canagliflozin may be associated with increased risk for bone fracture and risk for decreased bone mineral density	Canagliflozin (Invokana, Janssen), 300 mg	808	Excessive urination, including at night; increased thirst; constipation; and dry mouth
		Dapagliflozin (Farxiga, AstraZeneca), 10 mg	812	Excessive urination, including at night, and increased thirst
		Empagliflozin (Jardiance, Boehringer Ingelheim), 25 mg	812	Excessive urination, including at night, and increased thirst

CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; FDA = U.S. Food and Drug Administration; HbA_{1c} = hemoglobin A_{1c}; SGLT-2 = sodium–glucose cotransporter-2; SU = sulfonylurea; TZD = thiazolidinedione.
* Data obtained from https://healthcarebluebook.com.

therapy was of low rather than moderate quality. The committee also noted that the comparisons between metformin and metformin plus a sulfonylurea did not suggest greater cardiovascular mortality as the result of adding a sulfonylurea to metformin.

See the **Figure** for a summary of the recommendations and clinical considerations. **Appendix Tables 1** to **3** (available at Annals.org) contain further details about the comparative effectiveness and safety evidence.

RECOMMENDATIONS

Recommendation 1: ACP recommends that clinicians prescribe metformin to patients with type 2 diabetes when pharmacologic therapy is needed to improve glycemic control. (Grade: strong recommendation; moderate-quality evidence)

Metformin is effective in reducing glycemic levels, is associated with weight loss and fewer hypoglycemic episodes, and is cheaper than most other pharmacologic agents. Although the evidence was considered low quality, metformin may have an advantage over sulfonylurea monotherapy in terms of cardiovascular mortality. Therefore, unless contraindicated, metformin is the drug of choice for patients with type 2 diabetes, in addition to lifestyle modification.

As defined by the FDA, metformin is contraindicated in patients with decreased tissue perfusion or hemodynamic instability, advanced liver disease, alcohol abuse, acute unstable congestive heart failure, or any

condition that might lead to lactic acidosis. However, the FDA recently concluded that metformin is safe in patients with mild kidney impairment and in some patients with moderate kidney impairment (but is contraindicated in those with an estimated glomerular filtration rate <30 mL/min/1.73 m^2) (137).

Recommendation 2: ACP recommends that clinicians consider adding a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin to improve glycemic control when a second oral therapy is considered. (Grade: weak recommendation; moderate-quality evidence.) ACP recommends that clinicians and patients select among medications after discussing benefits, adverse effects, and costs.

Combination therapies with metformin were more effective than metformin monotherapy in reducing HbA_{1c} levels, weight, and blood pressure in patients with type 2 diabetes. This recommendation is graded as weak because of the fine balance between benefits and harms for the various drug combinations. See Table 2 for a summary of the comparative benefits and harms of metformin combination therapies as well as the adverse effects and cost of each medication. The evidence review did not include therapies combining more than 2 agents. Combination therapies also were associated with an increased risk for adverse effects compared with monotherapy.

Sulfonylureas have been used for many years and are the least expensive oral agent to add to metformin. However, sulfonylureas, both alone and combined with other agents, are associated with an increased risk for mild, moderate, or severe hypoglycemia as well as weight gain. The evidence review did not address medication switching for patients currently taking sulfonylureas. Regarding patients whose glycemic levels are adequately controlled and who do not have adverse effects with sulfonylureas, keeping them on this drug may be reasonable.

The SGLT-2 inhibitors are favored over sulfonylureas as an add-on to metformin therapy in terms of cardiovascular mortality, HbA_{1c}, weight, systolic blood pressure, and heart rate and are favored over DPP-4 inhibitors as an add-on to metformin therapy in terms of weight and systolic blood pressure. As an add-on to metformin therapy, DPP-4 inhibitors are favored over sulfonylureas for long-term all-cause mortality, long-term cardiovascular mortality, and cardiovascular morbidity; over pioglitazone for short-term cardiovascular morbidity; and over sulfonylureas or thiazolidinediones for weight.

Each class of drugs is associated with adverse effects, which are summarized in Table 2. The FDA warned that the DPP-4 inhibitors saxagliptin and alogliptin may increase the risk for heart failure, especially in patients who already have heart or kidney disease (138). The SGLT-2 inhibitors are associated with an increased risk for genital mycotic infections. Sulfonylureas are associated with an increased risk for hypoglycemia.

Although this guideline addresses only oral pharmacologic therapy, patients with persistent hyperglycemia despite oral agents and lifestyle interventions may need insulin therapy.

HIGH-VALUE CARE

Oral pharmacologic therapy with metformin (unless contraindicated) is an effective management strategy. It is cheaper and more effective than most other pharmacologic agents and is associated with fewer adverse effects; of note, it does not result in weight gain. Adding a second agent to metformin may provide additional benefits; however, the increased cost may not always support the added benefit, particularly for the more expensive, newer medications.

INSUFFICIENT AREAS OF EVIDENCE

Insufficient evidence exists for clinical outcomes, including mortality, cardiovascular morbidity, and micro- or macrovascular outcomes, for most drugs and drug comparisons. The evidence review did not address whether patients who are already taking sulfonylureas and have stable HbA_{1c} levels should switch to another medication. No data exist regarding the best time to add oral therapies to lifestyle modifications.

From American College of Physicians and University of Pennsylvania Health System, Philadelphia, Pennsylvania; Massachusetts General Hospital, Boston, Massachusetts; and Oregon Health and Science University, Portland, Oregon.

Financial Support: Financial support for the development of this guideline comes exclusively from the ACP operating budget.

Disclosures: Dr. Barry reports grants, personal fees, and nonfinancial support from Informed Medical Decisions Foundation and Healthwise, both nonprofits, outside the submitted work. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M16-1860. All financial and intellectual disclosures of interest were declared and potential conflicts were discussed and managed. Drs. Boyd, Iorio, and Vijan were recused from voting on this guideline because of active intellectual conflicts. Dr. Manaker was recused from voting on this guideline because of an active indirect financial conflict. A record of disclosures and management of conflicts of interest is kept for each Clinical Guidelines Committee meeting and conference call and can be viewed at www.acponline.org/clinical_information/guidelines/guidelines/conflicts_cgc.htm.

Requests for Single Reprints: Amir Qaseem, MD, PhD, MHA, American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106; e-mail, aqaseem@acponline.org.

Current author addresses and author contributions are available at Annals.org.

References

1. **Centers for Disease Control and Prevention.** National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta: U.S. Department of Health and Human Services; 2014.
2. **National Institute of Diabetes and Digestive and Kidney Diseases.** Diabetes Overview. Bethesda: National Institute of Diabetes and Digestive and Kidney Diseases; 2008.
3. **Centers for Disease Control and Prevention.** National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States. 2011. Accessed at www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf on 26 September 2016.
4. **Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians.** Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012;156:218-31. [PMID: 22312141] doi:10.7326/0003-4819-156-3-201202070-00011
5. **Bolen S, Tseng E, Hutfless S, Segal JB, Suarez-Cuervo C, Berger Z, et al.** Diabetes Medications for Adults with Type 2 Diabetes: An Update. Comparative Effectiveness Review no. 173. (Prepared by the Johns Hopkins University Evidence-based Practice Center under contract no. 290-2012-00007-I.) Rockville: Agency for Healthcare Research and Quality; 2016.
6. **Maruthur NM, Tseng E, Hutfless S, Wilson LM, Suarez-Cuervo C, Berger Z, et al.** Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2016;164:740-51. [PMID: 27088241] doi:10.7326/M15-2650
7. **Qaseem A, Snow V, Owens DK, Shekelle P; Clinical Guidelines Committee of the American College of Physicians.** The development of clinical practice guidelines and guidance statements of the American College of Physicians: summary of methods. Ann Intern Med. 2010;153:194-9. [PMID: 20679562] doi:10.7326/0003-4819-153-3-201008030-00010
8. **Hong J, Zhang Y, Lai S, Lv A, Su Q, Dong Y, et al; SPREAD-DIMCAD Investigators.** Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care. 2013;36:1304-11. [PMID: 23230096] doi:10.2337/dc12-0719
9. **Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al; ADOPT Study Group.** Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006;355:2427-43. [PMID: 17145742]
10. **Andersson C, Olesen JB, Hansen PR, Weeke P, Norgaard ML, Jørgensen CH, et al.** Metformin treatment is associated with a low risk of mortality in diabetic patients with heart failure: a retrospective nationwide cohort study. Diabetologia. 2010;53:2546-53. [PMID: 20838985] doi:10.1007/s00125-010-1906-6
11. **Schramm TK, Gislason GH, Vaag A, Rasmussen JN, Folke F, Hansen ML, et al.** Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur Heart J. 2011;32:1900-8. [PMID: 21471135] doi:10.1093/eurheartj/ehr077
12. **Wheeler S, Moore K, Forsberg CW, Riley K, Floyd JS, Smith NL, et al.** Mortality among veterans with type 2 diabetes initiating metformin, sulfonylurea or rosiglitazone monotherapy. Diabetologia. 2013;56:1934-43. [PMID: 23797633] doi:10.1007/s00125-013-2958-1
13. **Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, et al.** Increase in overall mortality risk in patients with type 2 diabetes receiving glipizide, glyburide or glimepiride monotherapy versus metformin: a retrospective analysis. Diabetes Obes Metab. 2012;14:803-9. [PMID: 22486923] doi:10.1111/j.1463-1326.2012.01604.x
14. **Corrao G, Romio SA, Zambon A, Merlino L, Bosi E, Scavini M.** Multiple outcomes associated with the use of metformin and sulphonylureas in type 2 diabetes: a population-based cohort study in Italy. Eur J Clin Pharmacol. 2011;67:289-99. [PMID: 21088829] doi:10.1007/s00228-010-0939-6
15. **Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, et al.** The risk of developing coronary artery disease or congestive heart failure, and overall mortality, in type 2 diabetic patients receiving rosiglitazone, pioglitazone, metformin, or sulfonylureas: a retrospective analysis. Acta Diabetol. 2009;46:145-54. [PMID: 19194648] doi:10.1007/s00592-008-0090-3
16. **Wang CP, Lorenzo C, Espinoza SE.** Frailty attenuates the impact of metformin on reducing mortality in older adults with type 2 diabetes. J Endocrinol Diabetes Obes. 2014;2:1031.
17. **Johnson JA, Simpson SH, Toth EL, Majumdar SR.** Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with type 2 diabetes. Diabet Med. 2005;22:497-502. [PMID: 15787679]
18. **Bennett WL, Wilson LM, Bolen S, Maruthur N, Singh S, Chatterjee R, et al.** Oral Diabetes Medications for Adults with Type 2 Diabetes: An Update. AHRQ Comparative Effectiveness Review no. 27. Rockville: Agency for Healthcare Research and Quality; 2011.
19. **Derosa G, Maffioli P, Salvadeo SA, Ferrari I, Gravina A, Mereu R, et al.** Direct comparison among oral hypoglycemic agents and their association with insulin resistance evaluated by euglycemic hyperinsulinemic clamp: the 60's study. Metabolism. 2009;58:1059-66. [PMID: 19394976] doi:10.1016/j.metabol.2009.03.007
20. **Erdem G, Dogru T, Tasci I, Bozoglu E, Muhsiroglu O, Tapan S, et al.** The effects of pioglitazone and metformin on plasma visfatin levels in patients with treatment naive type 2 diabetes mellitus. Diabetes Res Clin Pract. 2008;82:214-8. [PMID: 18778865] doi:10.1016/j.diabres.2008.07.021
21. **Erem C, Ozbas HM, Nuhoglu I, Deger O, Civan N, Ersoz HO.** Comparison of effects of gliclazide, metformin and pioglitazone monotherapies on glycemic control and cardiovascular risk factors in patients with newly diagnosed uncontrolled type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes. 2014;122:295-302. [PMID: 24710641] doi:10.1055/s-0034-1370989
22. **Esposito K, Maiorino MI, Di Palo C, Gicchino M, Petrizzo M, Bellastella G, et al.** Effects of pioglitazone versus metformin on circulating endothelial microparticles and progenitor cells in patients with newly diagnosed type 2 diabetes–a randomized controlled trial. Diabetes Obes Metab. 2011;13:439-45. [PMID: 21255215] doi:10.1111/j.1463-1326.2011.01367.x
23. **Esteghamati A, Azizi R, Ebadi M, Noshad S, Mousavizadeh M, Afarideh M, et al.** The comparative effect of pioglitazone and metformin on serum osteoprotegerin, adiponectin and intercellular adhesion molecule concentrations in patients with newly diagnosed type 2 diabetes: a randomized clinical trial. Exp Clin Endocrinol Diabetes. 2015;123:289-95. [PMID: 25607338] doi:10.1055/s-0034-1396864
24. **Esteghamati A, Ghasemiesfe M, Mousavizadeh M, Noshad S, Nakhjavani M.** Pioglitazone and metformin are equally effective in reduction of chemerin in patients with type 2 diabetes. J Diabetes Investig. 2014;5:327-32. [PMID: 24843782] doi:10.1111/jdi.12157
25. **Fidan E, Onder Ersoz H, Yilmaz M, Yilmaz H, Kocak M, Karahan C, et al.** The effects of rosiglitazone and metformin on inflammation and endothelial dysfunction in patients with type 2 diabetes mellitus. Acta Diabetol. 2011;48:297-302. [PMID: 21424914] doi:10.1007/s00592-011-0276-y
26. **Genovese S, De Berardis G, Nicolucci A, Mannucci E, Evangelista V, Totani L, et al.** Effect of pioglitazone versus metformin on cardiovascular risk markers in type 2 diabetes. Adv Ther. 2013;30:190-202. [PMID: 23359066] doi:10.1007/s12325-013-0003-x

27. **Gupta AK, Smith SR, Greenway FL, Bray GA.** Pioglitazone treatment in type 2 diabetes mellitus when combined with portion control diet modifies the metabolic syndrome. Diabetes Obes Metab. 2009;11:330-7. [PMID: 19267711] doi:10.1111/j.1463-1326.2008.00965.x
28. **Hällsten K, Virtanen KA, Lönnqvist F, Sipilä H, Oksanen A, Viljanen T, et al.** Rosiglitazone but not metformin enhances insulin- and exercise-stimulated skeletal muscle glucose uptake in patients with newly diagnosed type 2 diabetes. Diabetes. 2002;51:3479-85. [PMID: 12453903]
29. **Iliadis F, Kadoglou NP, Hatzitolios A, Karamouzis M, Alevizos M, Karamitsos D.** Metabolic effects of rosiglitazone and metformin in Greek patients with recently diagnosed type 2 diabetes. In Vivo. 2007;21:1107-14. [PMID: 18210765]
30. **Kato T, Sawai Y, Kanayama H, Taguchi H, Terabayashi T, Taki F, et al.** Comparative study of low-dose pioglitazone or metformin treatment in Japanese diabetic patients with metabolic syndrome. Exp Clin Endocrinol Diabetes. 2009;117:593-9. [PMID: 19924605] doi:10.1055/s-0029-1202792
31. **Kiyici S, Ersoy C, Kaderli A, Fazlioglu M, Budak F, Duran C, et al.** Effect of rosiglitazone, metformin and medical nutrition treatment on arterial stiffness, serum MMP-9 and MCP-1 levels in drug naive type 2 diabetic patients. Diabetes Res Clin Pract. 2009;86:44-50. [PMID: 19674806] doi:10.1016/j.diabres.2009.07.004
32. **Lawrence JM, Reid J, Taylor GJ, Stirling C, Reckless JP.** Favorable effects of pioglitazone and metformin compared with gliclazide on lipoprotein subfractions in overweight patients with early type 2 diabetes. Diabetes Care. 2004;27:41-6. [PMID: 14693964]
33. **Pavo I, Jermendy G, Varkonyi TT, Kerenyi Z, Gyimesi A, Shoustov S, et al.** Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes. J Clin Endocrinol Metab. 2003;88:1637-45. [PMID: 12679450]
34. **Perez A, Zhao Z, Jacks R, Spanheimer R.** Efficacy and safety of pioglitazone/metformin fixed-dose combination therapy compared with pioglitazone and metformin monotherapy in treating patients with T2DM. Curr Med Res Opin. 2009;25:2915-23. [PMID: 19827910] doi:10.1185/03007990903350011
35. **Ramachandran A, Snehalatha C, Salini J, Vijay V.** Use of glimepiride and insulin sensitizers in the treatment of type 2 diabetes–a study in Indians. J Assoc Physicians India. 2004;52:459-63. [PMID: 15645955]
36. **Rosenstock J, Rood J, Cobitz A, Biswas N, Chou H, Garber A.** Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. Diabetes Obes Metab. 2006;8:650-60. [PMID: 17026489]
37. **Russell-Jones D, Cuddihy RM, Hanefeld M, Kumar A, González JG, Chan M, et al; DURATION-4 Study Group.** Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. Diabetes Care. 2012;35:252-8. [PMID: 22210563] doi:10.2337/dc11-1107
38. **Schernthaner G, Matthews DR, Charbonnel B, Hanefeld M, Brunetti P; Quartet Study Group.** Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial. J Clin Endocrinol Metab. 2004;89:6068-76. [PMID: 15579760]
39. **Taslimi S, Esteghamati A, Rashidi A, Tavakkoli HM, Nakhjavani M, Kebriaee-Zadeh A.** Treatment with pioglitazone is associated with decreased preprandial ghrelin levels: a randomized clinical trial. Peptides. 2013;40:89-92. [PMID: 23276779] doi:10.1016/j.peptides.2012.12.020
40. **Yamanouchi T, Sakai T, Igarashi K, Ichiyanagi K, Watanabe H, Kawasaki T.** Comparison of metabolic effects of pioglitazone, metformin, and glimepiride over 1 year in Japanese patients with newly diagnosed type 2 diabetes. Diabet Med. 2005;22:980-5. [PMID: 16026361]
41. **Yoon KH, Shin JA, Kwon HS, Lee SH, Min KW, Ahn YB, et al.** Comparison of the efficacy of glimepiride, metformin, and rosiglitazone monotherapy in korean drug-naïve type 2 diabetic patients: the practical evidence of antidiabetic monotherapy study. Diabetes Metab J. 2011;35:26-33. [PMID: 21537410] doi:10.4093/dmj.2011.35.1.26
42. **Teramoto T, Yamada N, Shirai K, Saito Y.** Effects of pioglitazone hydrochloride on Japanese patients with type 2 diabetes mellitus. J Atheroscler Thromb. 2007;14:86-93. [PMID: 17485893]
43. **Hanefeld M, Patwardhan R, Jones NP; Rosiglitazone Clinical Trials Study Group.** A one-year study comparing the efficacy and safety of rosiglitazone and glibenclamide in the treatment of type 2 diabetes. Nutr Metab Cardiovasc Dis. 2007;17:13-23. [PMID: 17174222]
44. **Jain R, Osei K, Kupfer S, Perez AT, Zhang J.** Long-term safety of pioglitazone versus glyburide in patients with recently diagnosed type 2 diabetes mellitus. Pharmacotherapy. 2006;26:1388-95. [PMID: 16999648]
45. **Nakamura T, Matsuda T, Kawagoe Y, Ogawa H, Takahashi Y, Sekizuka K, et al.** Effect of pioglitazone on carotid intima-media thickness and arterial stiffness in type 2 diabetic nephropathy patients. Metabolism. 2004;53:1382-6. [PMID: 15375799]
46. **Nakamura T, Ushiyama C, Shimada N, Hayashi K, Ebihara I, Koide H.** Comparative effects of pioglitazone, glibenclamide, and voglibose on urinary endothelin-1 and albumin excretion in diabetes patients. J Diabetes Complications. 2000;14:250-4. [PMID: 11113686]
47. **Bakris G, Viberti G, Weston WM, Heise M, Porter LE, Freed MI.** Rosiglitazone reduces urinary albumin excretion in type II diabetes. J Hum Hypertens. 2003;17:7-12. [PMID: 12571611]
48. **Pfützner A, Marx N, Lübben G, Langenfeld M, Walcher D, Konrad T, et al.** Improvement of cardiovascular risk markers by pioglitazone is independent from glycemic control: results from the pioneer study. J Am Coll Cardiol. 2005;45:1925-31. [PMID: 15963388]
49. **Tan M, Johns D, González Gálvez G, Antúnez O, Fabián G, Flores-Lozano F, et al; GLAD Study Group.** Effects of pioglitazone and glimepiride on glycemic control and insulin sensitivity in Mexican patients with type 2 diabetes mellitus: a multicenter, randomized, double-blind, parallel-group trial. Clin Ther. 2004;26:680-93. [PMID: 15220012]
50. **Tan MH, Johns D, Strand J, Halse J, Madsbad S, Eriksson JW, et al; GLAC Study Group.** Sustained effects of pioglitazone vs. glibenclamide on insulin sensitivity, glycaemic control, and lipid profiles in patients with type 2 diabetes. Diabet Med. 2004;21:859-66. [PMID: 15270789]
51. **Nakamura T, Sugaya T, Kawagoe Y, Ueda Y, Koide H.** Effect of pioglitazone on urinary liver-type fatty acid-binding protein concentrations in diabetes patients with microalbuminuria. Diabetes Metab Res Rev. 2006;22:385-9. [PMID: 16506273]
52. **Shihara N, Kitaoka M, Inagaki N, Kadowaki T, Koumoto S, Satoh J, et al.** Randomized controlled trial of single-agent glimepiride and pioglitazone in Japanese patients with type 2 diabetes: a comparative study. J Diabetes Investig. 2011;2:391-8. [PMID: 24843519] doi:10.1111/j.2040-1124.2011.00115.x
53. **Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE; Sitagliptin 036 Study Group.** Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. Diabetes Care. 2007;30:1979-87. [PMID: 17485570]
54. **Williams-Herman D, Johnson J, Teng R, Luo E, Davies MJ, Kaufman KD, et al.** Efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes: a 54-week study. Curr Med Res Opin. 2009;25:569-83. [PMID: 19232032] doi:10.1185/03007990802705679
55. **Aschner P, Katzeff HL, Guo H, Sunga S, Williams-Herman D, Kaufman KD, et al; Sitagliptin Study 049 Group.** Efficacy and safety of monotherapy of sitagliptin compared with metformin in patients with type 2 diabetes. Diabetes Obes Metab. 2010;12:252-61. [PMID: 20070351] doi:10.1111/j.1463-1326.2009.01187.x
56. **Jadzinsky M, Pfützner A, Paz-Pacheco E, Xu Z, Allen E, Chen R; CV181-039 Investigators.** Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized

controlled trial. Diabetes Obes Metab. 2009;11:611-22. [PMID: 19515181] doi:10.1111/j.1463-1326.2009.01056.x
57. **Pratley RE, Fleck P, Wilson C.** Efficacy and safety of initial combination therapy with alogliptin plus metformin versus either as monotherapy in drug-naïve patients with type 2 diabetes: a randomized, double-blind, 6-month study. Diabetes Obes Metab. 2014;16:613-21. [PMID: 24400655] doi:10.1111/dom.12258
58. **Williams-Herman D, Johnson J, Teng R, Golm G, Kaufman KD, Goldstein BJ, et al.** Efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy over 2 years in patients with type 2 diabetes. Diabetes Obes Metab. 2010;12:442-51. [PMID: 20415693] doi:10.1111/j.1463-1326.2010.01204.x
59. **Haak T, Meinicke T, Jones R, Weber S, von Eynatten M, Woerle HJ.** Initial combination of linagliptin and metformin improves glycaemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab. 2012;14:565-74. [PMID: 22356132] doi:10.1111/j.1463-1326.2012.01590.x
60. **Pfützner A, Paz-Pacheco E, Allen E, Frederich R, Chen R; CV181039 Investigators.** Initial combination therapy with saxagliptin and metformin provides sustained glycaemic control and is well tolerated for up to 76 weeks. Diabetes Obes Metab. 2011;13:567-76. [PMID: 21342412] doi:10.1111/j.1463-1326.2011.01385.x
61. **Barnett AH, Patel S, Harper R, Toorawa R, Thiemann S, von Eynatten M, et al.** Linagliptin monotherapy in type 2 diabetes patients for whom metformin is inappropriate: an 18-week randomized, double-blind, placebo-controlled phase III trial with a 34-week active-controlled extension. Diabetes Obes Metab. 2012;14:1145-54. [PMID: 22974280] doi:10.1111/dom.12011
62. **Arjona Ferreira JC, Corry D, Mogensen CE, Sloan L, Xu L, Golm GT, et al.** Efficacy and safety of sitagliptin in patients with type 2 diabetes and ESRD receiving dialysis: a 54-week randomized trial. Am J Kidney Dis. 2013;61:579-87. [PMID: 23352379] doi:10.1053/j.ajkd.2012.11.043
63. **Scott R, Loeys T, Davies MJ, Engel SS; Sitagliptin Study 801 Group.** Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes. Diabetes Obes Metab. 2008;10:959-69. [PMID: 18201203] doi:10.1111/j.1463-1326.2007.00839.x
64. **Henry RR, Murray AV, Marmolejo MH, Hennicken D, Ptaszynska A, List JF.** Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. Int J Clin Pract. 2012;66:446-56. [PMID: 22413962] doi:10.1111/j.1742-1241.2012.02911.x
65. **List JF, Woo V, Morales E, Tang W, Fiedorek FT.** Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care. 2009;32:650-7. [PMID: 19114612] doi:10.2337/dc08-1863
66. **Ferrannini E, Berk A, Hantel S, Pinnetti S, Hach T, Woerle HJ, et al.** Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: an active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. Diabetes Care. 2013;36:4015-21. [PMID: 24186878] doi:10.2337/dc13-0663
67. **Rosenstock J, Seman LJ, Jelaska A, Hantel S, Pinnetti S, Hach T, et al.** Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes Obes Metab. 2013;15:1154-60. [PMID: 23906374] doi:10.1111/dom.12185
68. **Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K, et al; Canagliflozin DIA 2001 Study Group.** Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care. 2012;35:1232-8. [PMID: 22492586] doi:10.2337/dc11-1926
69. **Lavalle-González FJ, Januszewicz A, Davidson J, Tong C, Qiu R, Canovatchel W, et al.** Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Diabetologia. 2013;56:2582-92. [PMID: 24026211] doi:10.1007/s00125-013-3039-1
70. **Rosenstock J, Hansen L, Zee P, Li Y, Cook W, Hirshberg B, et al.** Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. Diabetes Care. 2015;38:376-83. [PMID: 25352655] doi:10.2337/dc14-1142
71. **Del Prato S, Nauck M, Durán-Garcia S, Maffei L, Rohwedder K, Theuerkauf A, et al.** Long-term glycaemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in patients with type 2 diabetes: 4-year data. Diabetes Obes Metab. 2015;17:581-90. [PMID: 25735400] doi:10.1111/dom.12459
72. **Cefalu WT, Leiter LA, Yoon KH, Arias P, Niskanen L, Xie J, et al.** Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet. 2013;382:941-50. [PMID: 23850055] doi:10.1016/S0140-6736(13)60683-2
73. **Nauck MA, Del Prato S, Meier JJ, Durán-García S, Rohwedder K, Elze M, et al.** Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care. 2011;34:2015-22. [PMID: 21816980] doi:10.2337/dc11-0606
74. **Ridderstråle M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC; EMPA-REG H2H-SU trial investigators.** Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endocrinol. 2014;2:691-700. [PMID: 24948511] doi:10.1016/S2213-8587(14)70120-2
75. **Leiter LA, Yoon KH, Arias P, Langslet G, Xie J, Balis DA, et al.** Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. Diabetes Care. 2015;38:355-64. [PMID: 25205142] doi:10.2337/dc13-2762
76. **Rigby SP, Handelsman Y, Lai YL, Abby SL, Tao B, Jones MR.** Effects of colesevelam, rosiglitazone, or sitagliptin on glycemic control and lipid profile in patients with type 2 diabetes mellitus inadequately controlled by metformin monotherapy. Endocr Pract. 2010;16:53-63. [PMID: 19789153] doi:10.4158/EP09146.OR
77. **Chawla S, Kaushik N, Singh NP, Ghosh RK, Saxena A.** Effect of addition of either sitagliptin or pioglitazone in patients with uncontrolled type 2 diabetes mellitus on metformin: a randomized controlled trial. J Pharmacol Pharmacother. 2013;4:27-32. [PMID: 23662021] doi:10.4103/0976-500X.107656
78. **Bergenstal RM, Wysham C, Macconell L, Malloy J, Walsh B, Yan P, et al; DURATION-2 Study Group.** Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet. 2010;376:431-9. [PMID: 20580422] doi:10.1016/S0140-6736(10)60590-9
79. **DeFronzo RA, Burant CF, Fleck P, Wilson C, Mekki Q, Pratley RE.** Efficacy and tolerability of the DPP-4 inhibitor alogliptin combined with pioglitazone, in metformin-treated patients with type 2 diabetes. J Clin Endocrinol Metab. 2012;97:1615-22. [PMID: 22419732] doi:10.1210/jc.2011-2243
80. **Home PD, Jones NP, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, et al; RECORD Study Group.** Rosiglitazone RECORD study: glucose control outcomes at 18 months. Diabet Med. 2007;24:626-34. [PMID: 17517066]
81. **Bakris GL, Ruilope LM, McMorn SO, Weston WM, Heise MA, Freed MI, et al.** Rosiglitazone reduces microalbuminuria and blood pressure independently of glycemia in type 2 diabetes patients with microalbuminuria. J Hypertens. 2006;24:2047-55. [PMID: 16957566]
82. **Umpierrez G, Issa M, Vlajnic A.** Glimepiride versus pioglitazone combination therapy in subjects with type 2 diabetes inadequately controlled on metformin monotherapy: results of a randomized clinical trial. Curr Med Res Opin. 2006;22:751-9. [PMID: 16684436]
83. **Derosa G, Gaddi AV, Piccinni MN, Ciccarelli L, Salvadeo S, Peros E, et al.** Antithrombotic effects of rosiglitazone-metformin versus glimepiride-metformin combination therapy in patients with type 2

diabetes mellitus and metabolic syndrome. Pharmacotherapy. 2005; 25:637-45. [PMID: 15899724]
84. **Garber A, Klein E, Bruce S, Sankoh S, Mohideen P.** Metformin-glibenclamide versus metformin plus rosiglitazone in patients with type 2 diabetes inadequately controlled on metformin monotherapy. Diabetes Obes Metab. 2006;8:156-63. [PMID: 16448519]
85. **Maffioli P, Fogari E, D'Angelo A, Perrone T, Derosa G.** Ultrasonography modifications of visceral and subcutaneous adipose tissue after pioglitazone or glibenclamide therapy combined with rosuvastatin in type 2 diabetic patients not well controlled by metformin. Eur J Gastroenterol Hepatol. 2013;25:1113-22. [PMID: 23524525] doi:10.1097/MEG.0b013e3283608317
86. **Petrica L, Petrica M, Vlad A, Dragos Jianu C, Gluhovschi G, Ianculescu C, et al.** Nephro- and neuroprotective effects of rosiglitazone versus glimepiride in normoalbuminuric patients with type 2 diabetes mellitus: a randomized controlled trial. Wien Klin Wochenschr. 2009;121:765-75. [PMID: 20047115] doi:10.1007/s00508-009-1279-3
87. **Hamann A, Garcia-Puig J, Paul G, Donaldson J, Stewart M.** Comparison of fixed-dose rosiglitazone/metformin combination therapy with sulphonylurea plus metformin in overweight individuals with type 2 diabetes inadequately controlled on metformin alone. Exp Clin Endocrinol Diabetes. 2008;116:6-13. [PMID: 18095238]
88. **Roden M, Weng J, Eilbracht J, Delafont B, Kim G, Woerle HJ, et al; EMPA-REG MONO trial investigators.** Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol. 2013;1:208-19. [PMID: 24622369] doi:10.1016/S2213-8587(13)70084-6
89. **Rosenstock J, Inzucchi SE, Seufert J, Fleck PR, Wilson CA, Mekki Q.** Initial combination therapy with alogliptin and pioglitazone in drug-naïve patients with type 2 diabetes. Diabetes Care. 2010;33: 2406-8. [PMID: 20724648] doi:10.2337/dc10-0159
90. **St John Sutton M, Rendell M, Dandona P, Dole JF, Murphy K, Patwardhan R, et al.** A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycemic control in patients with type 2 diabetes. Diabetes Care. 2002;25:2058-64. [PMID: 12401757]
91. **Kaku K.** Efficacy and safety of therapy with metformin plus pioglitazone in the treatment of patients with type 2 diabetes: a double-blind, placebo-controlled, clinical trial. Curr Med Res Opin. 2009;25: 1111-9. [PMID: 19309251] doi:10.1185/03007990902820816
92. **Bailey CJ, Bagdonas A, Rubes J, McMorn SO, Donaldson J, Biswas N, et al.** Rosiglitazone/metformin fixed-dose combination compared with uptitrated metformin alone in type 2 diabetes mellitus: a 24-week, multicenter, randomized, double-blind, parallel-group study. Clin Ther. 2005;27:1548-61. [PMID: 16330291]
93. **Fonseca V, Rosenstock J, Patwardhan R, Salzman A.** Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. JAMA. 2000; 283:1695-702. [PMID: 10755495]
94. **Feinglos M, Dailey G, Cefalu W, Osei K, Tayek J, Canovatchel W, et al.** Effect on glycemic control of the addition of 2.5 mg glipizide GITS to metformin in patients with T2DM. Diabetes Res Clin Pract. 2005;68:167-75. [PMID: 15860246]
95. **Garber AJ, Donovan DS Jr, Dandona P, Bruce S, Park JS.** Efficacy of glyburide/metformin tablets compared with initial monotherapy in type 2 diabetes. J Clin Endocrinol Metab. 2003;88:3598-604. [PMID: 12915642]
96. **Goldstein BJ, Pans M, Rubin CJ.** Multicenter, randomized, double-masked, parallel-group assessment of simultaneous glipizide/metformin as second-line pharmacologic treatment for patients with type 2 diabetes mellitus that is inadequately controlled by a sulfonylurea. Clin Ther. 2003;25:890-903. [PMID: 12852706]
97. **Marre M, Howlett H, Lehert P, Allavoine T.** Improved glycaemic control with metformin-glibenclamide combined tablet therapy (Glucovance) in type 2 diabetic patients inadequately controlled on metformin. Diabet Med. 2002;19:673-80. [PMID: 12147149]
98. **Garber AJ, Larsen J, Schneider SH, Piper BA, Henry D; Glyburide/Metformin Initial Therapy Study Group.** Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. Diabetes Obes Metab. 2002;4:201-8. [PMID: 12047399]
99. **Hermann LS, Scherstén B, Bitzén PO, Kjellström T, Lindgärde F, Melander A.** Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations. A double-blind controlled study. Diabetes Care. 1994;17:1100-9. [PMID: 7821128]
100. **Hermann LS, Bitzén PO, Kjellström T, Lindgärde F, Scherstén B.** Comparative efficacy of metformin and glibenclamide in patients with non-insulin-dependent diabetes mellitus. Diabete Metab. 1991; 17:201-8. [PMID: 1936477]
101. **Charpentier G, Fleury F, Kabir M, Vaur L, Halimi S.** Improved glycaemic control by addition of glimepiride to metformin monotherapy in type 2 diabetic patients. Diabet Med. 2001;18:828-34. [PMID: 11678974]
102. **DeFronzo RA, Goodman AM.** Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med. 1995;333:541-9. [PMID: 7623902]
103. **Forst T, Uhlig-Laske B, Ring A, Graefe-Mody U, Friedrich C, Herbach K, et al.** Linagliptin (BI 1356), a potent and selective DPP-4 inhibitor, is safe and efficacious in combination with metformin in patients with inadequately controlled type 2 diabetes. Diabet Med. 2010;27:1409-19. [PMID: 21059094] doi:10.1111/j.1464-5491.2010.03131.x
104. **Bergenstal RM, Forti A, Chiasson JL, Woloschak M, Boldrin M, Balena R.** Efficacy and safety of taspoglutide versus sitagliptin for type 2 diabetes mellitus (T-emerge 4 trial). Diabetes Ther. 2012;3:13. [PMID: 23138449] doi:10.1007/s13300-012-0013-8
105. **Reasner C, Olansky L, Seck TL, Williams-Herman DE, Chen M, Terranella L, et al.** The effect of initial therapy with the fixed-dose combination of sitagliptin and metformin compared with metformin monotherapy in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2011;13:644-52. [PMID: 21410627] doi:10.1111/j.1463-1326.2011.01390.x
106. **Yang W, Pan CY, Tou C, Zhao J, Gause-Nilsson I.** Efficacy and safety of saxagliptin added to metformin in Asian people with type 2 diabetes mellitus: a randomized controlled trial. Diabetes Res Clin Pract. 2011;94:217-24. [PMID: 21871686] doi:10.1016/j.diabres.2011.07.035
107. **Yang W, Guan Y, Shentu Y, Li Z, Johnson-Levonas AO, Engel SS, et al.** The addition of sitagliptin to ongoing metformin therapy significantly improves glycemic control in Chinese patients with type 2 diabetes. J Diabetes. 2012;4:227-37. [PMID: 22672586] doi:10.1111/j.1753-0407.2012.00213.x
108. **Derosa G, Carbone A, D'Angelo A, Querci F, Fogari E, Cicero AF, et al.** Variations in inflammatory biomarkers following the addition of sitagliptin in patients with type 2 diabetes not controlled with metformin. Intern Med. 2013;52:2179-87. [PMID: 24088749]
109. **White JL, Buchanan P, Li J, Frederich R.** A randomized controlled trial of the efficacy and safety of twice-daily saxagliptin plus metformin combination therapy in patients with type 2 diabetes and inadequate glycemic control on metformin monotherapy. BMC Endocr Disord. 2014;14:17. [PMID: 24565221] doi:10.1186/1472-6823-14-17
110. **Ross SA, Rafeiro E, Meinicke T, Toorawa R, Weber-Born S, Woerle HJ.** Efficacy and safety of linagliptin 2.5 mg twice daily versus 5 mg once daily in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, placebo-controlled trial. Curr Med Res Opin. 2012;28:1465-74. [PMID: 22816729]
111. **Nauck MA, Ellis GC, Fleck PR, Wilson CA, Mekki Q; Alogliptin Study 008 Group.** Efficacy and safety of adding the dipeptidyl peptidase-4 inhibitor alogliptin to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a multicentre, randomised, double-blind, placebo-controlled study. Int J Clin Pract. 2009;63:46-55. [PMID: 19125992] doi:10.1111/j.1742-1241.2008.01933.x

112. **Taskinen MR, Rosenstock J, Tamminen I, Kubiak R, Patel S, Dugi KA, et al.** Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab. 2011;13:65-74. [PMID: 21114605] doi:10.1111/j.1463-1326.2010.01326.x
113. **Seino Y, Miyata Y, Hiroi S, Hirayama M, Kaku K.** Efficacy and safety of alogliptin added to metformin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial with an open-label, long-term extension study. Diabetes Obes Metab. 2012;14:927-36. [PMID: 22583697] doi:10.1111/j.1463-1326.2012.01620.x
114. **Nauck M, Weinstock RS, Umpierrez GE, Guerci B, Skrivanek Z, Milicevic Z.** Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). Diabetes Care. 2014;37:2149-58. [PMID: 24742660] doi:10.2337/dc13-2761
115. **Wang W, Yang J, Yang G, Gong Y, Patel S, Zhang C, et al.** Efficacy and safety of linagliptin in Asian patients with type 2 diabetes mellitus inadequately controlled by metformin: a multinational 24-week, randomized clinical trial. J Diabetes. 2016;8:229-37. [PMID: 25753488] doi:10.1111/1753-0407.12284
116. **Qiu R, Capuano G, Meininger G.** Efficacy and safety of twice-daily treatment with canagliflozin, a sodium glucose co-transporter 2 inhibitor, added on to metformin monotherapy in patients with type 2 diabetes mellitus. J Clin Transl Endocrinol. 2014;1:54-60.
117. **Häring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Broedl UC, et al; EMPA-REG MET Trial Investigators.** Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care. 2014;37:1650-9. [PMID: 24722494] doi:10.2337/dc13-2105
118. **Arechavaleta R, Seck T, Chen Y, Krobot KJ, O'Neill EA, Duran L, et al.** Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab. 2011;13:160-8. [PMID: 21199268] doi:10.1111/j.1463-1326.2010.01334.x
119. **Forst T, Anastassiadis E, Diessel S, Löffler A, Pfützner A.** Effect of linagliptin compared with glimepiride on postprandial glucose metabolism, islet cell function and vascular function parameters in patients with type 2 diabetes mellitus receiving ongoing metformin treatment. Diabetes Metab Res Rev. 2014;30:582-9. [PMID: 24459063] doi:10.1002/dmrr.2525
120. **Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP; Sitagliptin Study 024 Group.** Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab. 2007;9:194-205. [PMID: 17300595]
121. **Schernthaner G, Durán-Garcia S, Hanefeld M, Langslet G, Niskanen L, Östgren CJ, et al.** Efficacy and tolerability of saxagliptin compared with glimepiride in elderly patients with type 2 diabetes: a randomized, controlled study (GENERATION). Diabetes Obes Metab. 2015;17:630-8. [PMID: 25761977] doi:10.1111/dom.12461
122. **Schumm-Draeger PM, Burgess L, Korányi L, Hruba V, Hamer-Maansson JE, de Bruin TW.** Twice-daily dapagliflozin co-administered with metformin in type 2 diabetes: a 16-week randomized, placebo-controlled clinical trial. Diabetes Obes Metab. 2015;17:42-51. [PMID: 25200570] doi:10.1111/dom.12387
123. **Derosa G, Cicero AF, Franzetti IG, Querci F, Carbone A, Ciccarelli L, et al.** Effects of exenatide and metformin in combination on some adipocytokine levels: a comparison with metformin monotherapy. Can J Physiol Pharmacol. 2013;91:724-32. [PMID: 23984793] doi:10.1139/cjpp-2012-0300
124. **Forst T, Michelson G, Ratter F, Weber MM, Anders S, Mitry M, et al.** Addition of liraglutide in patients with type 2 diabetes well controlled on metformin monotherapy improves several markers of vascular function. Diabet Med. 2012;29:1115-8. [PMID: 22288732] doi:10.1111/j.1464-5491.2012.03589.x
125. **Blonde L, Rosenstock J, Mooradian AD, Piper BA, Henry D.** Glyburide/metformin combination product is safe and efficacious in patients with type 2 diabetes failing sulphonylurea therapy. Diabetes Obes Metab. 2002;4:368-75. [PMID: 12406033]
126. **Chien HH, Chang CT, Chu NF, Hsieh SH, Huang YY, Lee IT, et al.** Effect of glyburide-metformin combination tablet in patients with type 2 diabetes. J Chin Med Assoc. 2007;70:473-80. [PMID: 18063500]
127. **Kim HS, Kim DM, Cha BS, Park TS, Kim KA, Kim DL, et al.** Efficacy of glimepiride/metformin fixed-dose combination vs metformin uptitration in type 2 diabetic patients inadequately controlled on low-dose metformin monotherapy: a randomized, open label, parallel group, multicenter study in Korea. J Diabetes Investig. 2014;5:701-8. [PMID: 25422771] doi:10.1111/jdi.12201
128. **Ahrén B, Johnson SL, Stewart M, Cirkel DT, Yang F, Perry C, et al; HARMONY 3 Study Group.** HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. Diabetes Care. 2014;37:2141-8. [PMID: 24898304] doi:10.2337/dc14-0024
129. **Gupta A, Ansari NA, Yadav N.** Comparative efficacy and safety of sitagliptin and glimepiride in patients of newly diagnosed type 2 diabetes mellitus. Int J Pharm Sci Rev Res. 2013;23:137-41.
130. **Göke B, Gallwitz B, Eriksson J, Hellqvist A, Gause-Nilsson I; D1680C00001 Investigators.** Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial. Int J Clin Pract. 2010;64:1619-31. [PMID: 20846286] doi:10.1111/j.1742-1241.2010.02510.x
131. **Seck T, Nauck M, Sheng D, Sunga S, Davies MJ, Stein PP, et al; Sitagliptin Study 024 Group.** Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study. Int J Clin Pract. 2010;64:562-76. [PMID: 20456211] doi:10.1111/j.1742-1241.2010.02353.x
132. **Gallwitz B, Rosenstock J, Rauch T, Bhattacharya S, Patel S, von Eynatten M, et al.** 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. Lancet. 2012;380:475-83. [PMID: 22748821] doi:10.1016/S0140-6736(12)60691-6
133. **Del Prato S, Camisasca R, Wilson C, Fleck P.** Durability of the efficacy and safety of alogliptin compared with glipizide in type 2 diabetes mellitus: a 2-year study. Diabetes Obes Metab. 2014;16:1239-46. [PMID: 25132212] doi:10.1111/dom.12377
134. **Tolman KG, Freston JW, Kupfer S, Perez A.** Liver safety in patients with type 2 diabetes treated with pioglitazone: results from a 3-year, randomized, comparator-controlled study in the US. Drug Saf. 2009;32:787-800. [PMID: 19670918] doi:10.2165/11316510-000000000-00000
135. **Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF.** Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC Med. 2013;11:43. [PMID: 23425012] doi:10.1186/1741-7015-11-43
136. **Bolinder J, Ljunggren Ö, Johansson L, Wilding J, Langkilde AM, Sjöström CD, et al.** Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. Diabetes Obes Metab. 2014;16:159-69. [PMID: 23906445] doi:10.1111/dom.12189
137. **U.S. Food and Drug Administration.** FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. 2016. Accessed at www.fda.gov/Drugs/DrugSafety/ucm493244.htm on 26 September 2016.
138. **U.S. Food and Drug Administration.** FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin. 2016. Accessed at www.fda.gov/Drugs/DrugSafety/ucm486096.htm on 26 September 2016.

Current Author Addresses: Dr. Qaseem: American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106.
Dr. Barry: Massachusetts General Hospital, 50 Staniford Street, Boston, MA 02114.
Dr. Humphrey: Oregon Health and Science University, 3710 Southwest U.S. Veterans Hospital Road, Portland, OR 97201.
Dr. Forciea: University of Pennsylvania Health System, 3615 Chestnut Street, Philadelphia, PA 19104.

Author Contributions: Conception and design: A. Qaseem, M.J. Barry, L.L. Humphrey, N. Fitterman.
Analysis and interpretation of the data: A. Qaseem, M.J. Barry, L.L. Humphrey, N. Fitterman, D. Kansagara.
Drafting of the article: A. Qaseem.
Critical revision for important intellectual content: A. Qaseem, M.J. Barry, L.L. Humphrey, D. Kansagara.
Final approval of the article: A. Qaseem, M.J. Barry, L.L. Humphrey, M.A. Forciea, N. Fitterman, C. Horwitch, D. Kansagara, R. McLean, T. Wilt.
Statistical expertise: A. Qaseem.
Administrative, technical, or logistic support: A. Qaseem.
Collection and assembly of data: A. Qaseem.

Appendix: Methods

Key Questions Addressed

Key Question 1

a. In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative effectiveness of the specified monotherapy FDA-approved diabetes medications for the intermediate outcomes of HbA_{1c}, weight, systolic blood pressure, and heart rate?

b. In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative effectiveness of the specified metformin-based combinations of FDA-approved diabetes medications for the intermediate outcomes of HbA_{1c}, weight, systolic blood pressure, and heart rate?

Key Question 2

a. In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative effectiveness of the specified monotherapy FDA-approved diabetes medications for the long-term clinical outcomes of all-cause mortality, cardiovascular and cerebrovascular morbidity and mortality, retinopathy, nephropathy, and neuropathy?

b. In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative effectiveness of the specified metformin-based combinations of FDA-approved diabetes medications for the long-term clinical outcomes of all-cause mortality, cardiovascular and cerebrovascular morbidity and mortality, retinopathy, nephropathy, and neuropathy?

Key Question 3

a. In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative safety of the specified monotherapy FDA-approved diabetes medications regarding liver injury, lactic acidosis, pancreatitis, hypoglycemia, congestive heart failure, cancer, severe allergic reactions, macular edema or decreased vision, and gastrointestinal side effects; for comparisons including SGLT-2 inhibitors, what is the comparative safety regarding urinary tract infections, impaired renal function, genital mycotic infections, fracture, and volume depletion?

b. In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative safety of the specified metformin-based combinations of FDA-approved diabetes medications regarding liver injury, lactic acidosis, pancreatitis, hypoglycemia, congestive heart failure, cancer, severe allergic reactions, macular edema or decreased vision, and gastrointestinal side effects; for comparisons including SGLT-2 inhibitors, what is the comparative safety regarding urinary tract infections, impaired renal function, genital mycotic infections, fracture, and volume depletion?

Key Question 4

Do the comparative safety and effectiveness of these treatments differ across subgroups defined by the age, sex, race/ethnicity, and body mass index of adults with type 2 diabetes?

Search Strategy

To update the 2011 systematic review (18), the reviewers searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials for English-language studies published from April 2009 through March 2015 and updated through December 2015. Studies were limited to randomized, controlled trials for key question 1; high-quality observational studies also were considered for key questions 2 and 3.

Meta-analysis

The reviewers conducted a meta-analysis when data were sufficient and studies were sufficiently homogeneous with respect to study population characteristics, study duration, and medication dosing.

Quality Assessment

The reviewers used the Jadad criteria (139) to assess risk of bias in randomized, controlled trials and the Downs and Black tool (140) to assess nonrandomized trials and observational studies.

Population Studied

The study population included adults with type 2 diabetes, non–insulin-dependent diabetes mellitus, or adult-onset diabetes.

Interventions Evaluated

Evaluated pharmacologic interventions included metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, and SGLT-2 inhibitors. Although the GLP-1 receptor agonists were not evaluated in the guideline, they were included in the full evidence review (5).

Comparators

Monotherapies were compared with one another, metformin was compared with combination therapies including metformin, and metformin-based combination therapies were compared with one another.

Outcomes

Outcomes evaluated included all-cause mortality, cardiovascular and cerebrovascular morbidity and mortality, retinopathy, nephropathy, neuropathy, HbA_{1c}, weight, systolic blood pressure, heart rate, and harms.

Timing

In the studies evaluated, oral pharmacologic interventions were used for more than 3 months.

Setting

The setting was outpatient as well as inpatient.

Target Audience

The target audience for this guideline includes all clinicians.

Target Patient Population

The target patient population includes all adults with type 2 diabetes.

Peer Review

The AHRQ evidence review was sent to invited peer reviewers and posted on the AHRQ Web site for public comments, and the published review article was peer reviewed through the journal. The guideline was peer reviewed through the journal and posted online for comments from ACP Regents and ACP Governors, who represent physician members at the regional level.

Web-Only References

139. **Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al.** Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1-12. [PMID: 8721797]

140. **Downs SH, Black N.** The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52:377-84. [PMID: 9764259]

Appendix Table 1. Summary of Clinical Outcomes for Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus

Intervention*, by Outcome	Strength of Evidence	Studies, *n*	Summary†
All-cause mortality			
Monotherapy vs. monotherapy			
Metformin vs. pioglitazone	Low	5	Neither treatment favored for short-term mortality
Metformin vs. rosiglitazone	Low	4	Metformin favored
Metformin vs. SU (shorter-duration studies)	Low	4	Neither favored for short-term mortality
Metformin vs. SU (longer-duration studies)	Low	9	Metformin favored for long-term mortality
Metformin vs. DPP-4 inhibitors	Low	6	Neither treatment favored for short-term mortality
Metformin vs. SGLT-2 inhibitors	Low	4	Neither treatment favored
Pioglitazone vs. DPP-4 inhibitors	Low	2	Neither treatment favored
SU vs. DPP-4 inhibitors	Low	1	DPP-4 inhibitors favored for short-term mortality
Metformin vs. metformin combination			
Metformin vs. metformin + rosiglitazone	Low	6	Metformin monotherapy favored; OR, 2.51 (95% CI, 0.66–9.52) ‡
Metformin vs. metformin + SU	Low	5	Neither treatment favored for short-term mortality
Metformin vs. metformin + DPP-4 inhibitors (<2 y)	Low	14	Neither treatment favored for short-term mortality
Metformin vs. metformin + SGLT-2 inhibitors (shorter duration)	Low	6	Neither treatment favored for short-term mortality
Metformin vs. metformin + SGLT-2 inhibitors (long-duration studies)	Low	2	Neither treatment favored
Combination vs. combination			
Metformin + rosiglitazone vs. metformin + SU	Low	3	Neither treatment favored for short-term mortality
Metformin + SU vs. metformin + DPP-4 inhibitors (longer duration)	Low	6	Metformin + DPP-4 inhibitors favored for long-term mortality; OR, 0.64 (CI, 0.27–1.52) ‡
Metformin + SU vs. metformin + SGLT-2 inhibitors (longer duration)	Low	3	Neither treatment favored for long-term mortality
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	Low	2	Neither favored for short-term mortality
Cardiovascular mortality			
Monotherapy vs. monotherapy			
Metformin vs. pioglitazone	Low	2	Neither treatment favored
Metformin vs. rosiglitazone	Low	1	Neither treatment favored
Metformin vs. SU (longer-duration studies)	Moderate§	5	Metformin favored; range in RR from RCTs, 0.6–0.7; adjusted HR from observational studies, 0.6–0.9
Metformin vs. DPP-4 inhibitors	Low	3	DPP-4 inhibitors favored for short-term mortality
Rosiglitazone vs. SU (longer-duration studies)	Low	1	Rosiglitazone favored
Metformin vs. metformin combination			
Metformin vs. metformin + rosiglitazone	Low	5	Metformin favored for short-term mortality
Metformin vs. metformin + DPP-4 inhibitor	Low	7	Metformin + DPP-4 inhibitors favored for short-term mortality
Combination vs. combination			
Metformin + SU vs. metformin + DPP-4 inhibitors (104 wk follow-up)	Low	5	Metformin + DPP-4 inhibitors favored for long-term CVD mortality
Metformin + SU vs. metformin + SGLT-2 inhibitor (longer-duration studies)	Low	2	Metformin + SGLT-2 inhibitors favored
Cardiovascular morbidity			
Monotherapy vs. monotherapy			
Metformin vs. rosiglitazone	Low	5	Metformin favored for long-term CVD morbidity
Metformin vs. pioglitazone	Low	5	Neither treatment favored
Metformin vs. SU	Low	7	Metformin favored for long-term CVD morbidity; range in RR from RCTs, 0.7–1.6; adjusted HR from observational studies, 0.3–0.9
Rosiglitazone vs. SU	Low	4	SU favored for long-term CVD morbidity
Pioglitazone vs. SU	Low	3	Pioglitazone favored for short-term CVD morbidity
SU vs. DPP-4 inhibitors	Low	2	DPP-4 inhibitor favored for short-term CVD morbidity
Metformin vs. metformin combination			
Metformin vs. metformin + rosiglitazone (shorter duration)	Low	6	Metformin favored for short-term CVD morbidity
Metformin vs. metformin + SU (shorter duration)	Low	1	Metformin favored for short-term CVD morbidity
Metformin vs. metformin + SGLT-2 inhibitor (shorter duration)	Low	1	Metformin favored for short-term CVD
Combination vs. combination			
Metformin + pioglitazone vs. metformin + DPP-4 inhibitor (shorter duration)	Low	2	Metformin + DPP-4 inhibitor favored for short-term cardiovascular morbidity
Metformin + rosiglitazone vs. metformin + DPP-4 inhibitor (shorter duration)	Low	2	Metformin + rosiglitazone favored for short-term CVD morbidity
Metformin + SU vs. metformin + DPP-4 inhibitor (long-term nonfatal MI)	Low	2	Metformin + DPP-4 inhibitor favored for long-term nonfatal MI
Metformin + SU vs. metformin + SGLT-2 inhibitor (long-term)	Low	1	Neither favored

(*Continued on following page*)

Appendix Table 1–Continued

Intervention*, by Outcome	Strength of Evidence	Studies, *n*	Summary†
Nephropathy			
Monotherapy vs. monotherapy			
Metformin vs. SU (shorter-duration studies)	Low	4	Metformin favored
TZD vs. SU (mainly shorter-duration studies)	Low	7	TZD favored for short-term nephropathy outcomes
SU vs. DPP-4 inhibitors (shorter-duration study)	Low	1	Neither treatment favored
Metformin vs. metformin combination			
Metformin + TZD vs. metformin + SU (shorter-duration study)	Low	2	Metformin + TZD favored
Metformin + TZD vs. metformin + DPP-4 (shorter-duration study)	Low	1	Neither treatment favored
Neuropathy			
Metformin vs. metformin + DPP-4 inhibitor (shorter-duration study)	Low	1	Metformin favored
Metformin + TZD vs. metformin + SU (shorter-duration study)	Low	1	Neither treatment favored

CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; HR = hazard ratio; MI = myocardial infarction; OR = odds ratio; RCT = randomized, controlled trial; RR = relative risk; SGLT-2 = sodium–glucose cotransporter-2; SU = sulfonylurea; TZD = thiazolidinedione.
* Only comparisons that were evaluated by at least 1 randomized controlled trial are listed. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the clinical outcomes are short term (1 y or shorter), because few longer-duration studies evaluated this outcome.
† Unless otherwise specified, the estimates are the pooled mean between-group differences (95% CIs).
‡ Effect is not statistically significant.
§ Grade given by the evidence reviewers. The Clinical Guidelines Committee reviewed the individual studies and found the 2 trials to be underpowered, with no significant reductions in cardiovascular mortality with metformin versus sulfonylureas, and therefore considered the quality of evidence to be low.

Appendix Table 2. Summary of Intermediate Outcomes for Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus

Intervention, by Outcome	Strength of Evidence*	Studies, *n*	Summary†
HbA_{1c}			
Monotherapy vs. monotherapy			
Metformin vs. TZD	High	23	Neither drug favored; −0.04% (95% CI, −0.11 to 0.03%)
Metformin vs. SU	High	NA	No significant between-group differences (not updated for this report)
Metformin vs. DPP-4 inhibitors	High	6	Metformin favored; −0.43% (CI, −0.55 to −0.31%)
TZD vs. SU	High	15	Neither drug favored; −0.04% (CI, −0.13 to 0.06%)
SU vs. DPP-4 inhibitors	Moderate	3	SU favored; −0.21% (CI, −0.32 to −0.09%)
Metformin vs. metformin combination			
Metformin vs. metformin + TZD (HbA_{1c} ≥8%)	High	7	Metformin +TZD favored; 0.88% (CI, 0.73 to 1.04%)
Metformin vs. metformin + TZD (HbA_{1c} <8%)	High	7	Metformin + TZD favored; 0.43% (CI, 0.23 to 0.63%)
Metformin vs. metformin + SU	High	15	Metformin + SU favored; 0.94% (CI, 0.68 to 1.19%)
Metformin vs. metformin + DPP-4 inhibitors (shorter duration)	High	26	Metformin + DPP-4 inhibitor favored; 0.65% (CI, 0.60 to 0.70%)
Metformin vs. metformin + DPP-4 inhibitors (longer duration)	Moderate	4	Metformin + DPP-4 inhibitor favored; 0.5% (CI, 0.47 to 0.6%)
Metformin vs. metformin + SGLT-2 inhibitors	High	9	Metformin + SGLT-2 inhibitor favored; 0.61% (CI, 0.52 to 0.71%)
Combination vs. combination			
Metformin + TZD vs. metformin + SU	Moderate	8	Neither drug combination favored; −0.06% (CI, −0.19 to 0.06)
Metformin + TZD vs. metformin +DPP-4 inhibitors	Moderate	5	Metformin + TZD favored; −0.12% (CI, −0.21 to −0.02%)
Metformin + SU vs. metformin + SGLT-2 inhibitors (longer duration)	Moderate	3	Metformin + SGLT-2 inhibitor favored; 0.17% (CI, 0.10 to 0.20%)
Metformin + DPP-4 inhibitors vs. metformin +SGLT-2 inhibitors	Moderate	4	Metformin + SGLT-2 inhibitor favored; 0.17% (CI, 0.08 to 0.26%)
Weight			
Monotherapy vs. monotherapy			
Metformin vs. TZD	High	NA	Metformin favored; −2.6 kg (CI, −4.1 to −1.2 kg) (did not update for this report)
Metformin vs. SU	High	NA	Metformin favored; −2.7 kg (CI, −3.5 to −1.9 kg) (did not update for this report)
Metformin vs. DPP-4 inhibitors	High	6	Metformin favored; −1.3 kg (CI, −1.6 to −1.0 kg)
Metformin vs. SGLT-2 inhibitors	Moderate	3	SGLT-2 inhibitors favored; range of between-group differences, −1.3 to −1.4 kg
TZD vs. SU	High	7	SU favored; 1.2 kg (CI, 0.6 to 1.8 kg)
TZD vs. DPP-4 inhibitors	Moderate	2	DPP-4 inhibitors favored; range in between-group differences, −2.3 to −2.5 kg
DPP-4 inhibitors vs. SGLT-2 inhibitors	Moderate	1	SGLT-2 inhibitors favored; between-group difference, −2.5 to −2.7 kg
SU vs. DPP-4 inhibitors	Moderate	4	DPP-4 inhibitors favored; between-group difference, 0.7 to 1.8 kg
Metformin vs. metformin combination			
Metformin vs. metformin + TZD	High	6	Metformin favored; −2.2 kg (CI, −2.6 to −1.9 kg)
Metformin vs. metformin + SU	High	10	Metformin favored Baseline weight ≥90 kg; profile likelihood estimate: −3.2 kg (CI, −4.6 to −1.6 kg) Baseline weight <90 kg: −1.2 kg (CI, −1.6 to −0.6 kg)
Metformin vs. metformin + DPP-4 inhibitors (duration ≤1 y)	High	20	Neither treatment favored; −0.10 kg (CI, −0.30 to 0.01 kg)
Metformin vs. metformin + SGLT-2 inhibitors	High	7	Metformin + SGLT-2 inhibitors favored; 2.0 kg (CI, 1.5 to 2.5 kg)
Combination vs. combination			
Metformin + TZD vs. metformin + SU	Moderate	6	Metformin + SU favored; 0.9 kg (CI, 0.4 to 1.3 kg)
Metformin + TZD vs. metformin + DPP-4 inhibitors	Moderate	4	Metformin + DPP-4 inhibitors favored; 2.7 kg (CI, 0.8 to 4.5 kg)
Metformin + SU vs. metformin + DPP-4 inhibitors (duration <1 y)	High	4	Metformin + DPP-4 inhibitors favored; 2.2 kg (CI, 1.8 to 2.5 kg)
Metformin + SU vs. metformin + SGLT-2 inhibitors (longer duration)	High	3	Metformin + SGLT-2 inhibitors favored; 4.7 kg (CI, 4.4 to 5.0 kg)
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	Moderate	5	Metformin + SGLT-2 inhibitors favored; range in between-group differences, −1.8 to −3.6 kg

(*Continued on following page*)

Appendix Table 2–Continued

Intervention, by Outcome	Strength of Evidence*	Studies, *n*	Summary†
Systolic blood pressure			
Monotherapy vs. monotherapy			
Metformin vs. SGLT-2 inhibitors	Moderate	4	SGLT-2 inhibitors favored; 2.8 mm Hg (CI, 2.6 to 3.0 mm Hg)
Metformin vs. metformin combination			
Metformin vs. metformin + SGLT-2 inhibitors (shorter duration)	High	7	Metformin + SGLT-2 inhibitors favored; 4.4 mm Hg (CI, 2.9 to 6.0 mm Hg)
Combination vs. combination			
Metformin + SU vs. metformin + SGLT-2 inhibitors (longer duration)	High	3	Metformin + SGLT-2 inhibitors favored; 5.1 mm Hg (CI, 4.2 to 6.0 mm Hg)
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	Moderate	4	Metformin + SGLT-2 inhibitors favored; 4.1 mm Hg (CI, 3.6 to 4.6 mm Hg)
Heart rate			
Combination vs. combination			
Metformin + SU vs. metformin +SGLT-2 inhibitors (longer duration)	Moderate	3	Metformin + SGLT-2 inhibitor favored; mean between-group difference, 1.5 beats/min (CI, 0.6 to 2.3 beats/min)

DPP-4 = dipeptidyl peptidase-4; HbA_{1c} = hemoglobin A_{1c}; NA = not applicable; SGLT-2 = sodium–glucose cotransporter-2; SU = sulfonylurea; TZD = thiazolidinedione.
* This table summarizes only high- and moderate-quality evidence.
† Unless otherwise specified, the estimates are the pooled mean between-group differences (95% CIs).

Appendix Table 3. Summary of Harms for Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus

Intervention, by Outcome	Strength of Evidence	Studies, *n*	Summary*
Hypoglycemia			
Monotherapy vs. monotherapy			
Metformin vs. TZD			
Mild, moderate, total symptoms	Low	5	Metformin favored
Severe symptoms	Low	1	Neither favored
Metformin vs. SU			
Mild, moderate symptoms	High	5	Metformin favored; OR, 2.59 (95% CI, 0.98 to 8.86)†
Severe symptoms	Moderate	3	Metformin favored; OR, 1.4 to 2; RD, 0.8% to 14% OR in normal renal function, 9.0 (CI, 4.9 to 16.4), and in impaired renal function, 6.0 (CI, 3.8 to 9.5)
Metformin vs. DPP-4 inhibitors			
Mild, moderate, total symptoms	Low	6	DPP-4 inhibitor favored
Severe symptoms	Low	6	Neither favored
Metformin vs. SGLT-2 inhibitors			
Mild, moderate symptoms	Moderate	4	SGLT-2 inhibitors favored; OR, 0.46 (CI, 0.16 to 1.30)†
Severe symptoms	Moderate	3	Neither favored
TZD vs. SU			
Mild, moderate symptoms	High	5	TZD favored; OR, 6.31 (CI, 4.08 to 9.76)
Severe symptoms	Moderate	2	TZD favored; OR, 8.0; RD, 0.5%
TZD vs. DPP-4 inhibitors			
Severe symptoms	Low	2	Neither favored
SU vs. DPP-4 inhibitors			
Mild, moderate, total symptoms	Moderate	4	DPP-4 favored; range in OR, 3.8 to 12.4; range in RD, 6% to 15%
Severe symptoms	Moderate	2	DPP-4 favored
DPP-4 inhibitors vs. SGLT-2 inhibitors			
Mild, moderate, total symptoms	Low	1	Neither favored
Severe symptoms	Low	1	Neither favored
Metformin vs. metformin combination			
Metformin vs. metformin + TZD			
Mild, moderate, total symptoms	High	8	Metformin favored; OR, 1.56 (CI, 0.99 to 2.44)†
Metformin vs. metformin + SU			
Mild, moderate, total symptoms	Moderate	10	Metformin favored, range in OR, 2 to 17; range in RD, 0% to 35%
Severe symptoms	Moderate	2	Neither favored
Metformin vs. metformin + DPP-4 inhibitors			
Mild, moderate symptoms	High	14	Neither favored; pooled OR for mild–moderate, 0.97 (CI, 0.6 to 1.5)
Severe symptoms	High	12	Neither favored
Metformin vs. metformin + SGLT-2 inhibitors (<2 y)			
Mild, moderate symptoms	Moderate	7	Metformin favored; OR, 1.74 (CI, 0.83 to 3.66)†
Severe symptoms	Moderate	7	Neither favored; no events
Combination vs. combination			
Metformin + TZD vs. metformin + SU			
Mild, moderate symptoms	High	6	Metformin + TZD favored; OR, 7.45 (CI, 4.02 to 13.81)
Severe symptoms	Low	1	Metformin + TZD favored
Metformin + TZD vs. metformin + DPP-4 inhibitors			
Mild, moderate, total symptoms	Low	2	Neither drug combination favored
Severe symptoms	Low	3	Neither favored
Metformin + SU vs. metformin + DPP-4 inhibitors			
Mild, moderate symptoms	High	4	Metformin + DPP4-inhibitors favored; OR, 0.27 (CI, 0.18 to 0.39)
Severe symptoms	High	7	Metformin + DPP-4 favored <52 wk: OR, 0.2 (CI, 0.1 to 0.6) ≥52 wk: OR, 0.1 (CI, 0.03 to 0.3)
Metformin + SU vs. metformin + SGLT-2 inhibitors (<2 y)			
Mild, moderate, total symptoms	High	3	Metformin + SGLT-2 inhibitors favored; OR, 0.08 (CI, 0.03 to 0.17)
Severe symptoms	Moderate	2	Metformin + SGLT-2 inhibitors; OR, 7; range in RD, 1% to 13%
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors			
Mild, moderate, total symptoms	Low	4	Neither group favored in studies lasting 12–78 wk
Severe symptoms	Low	2	Neither group favored

(*Continued on following page*)

Appendix Table 3–Continued

Intervention, by Outcome	Strength of Evidence	Studies, *n*	Summary*
GI side effects			
Monotherapy vs. monotherapy			
Metformin vs. TZD	Moderate	6	TZD favored for diarrhea: OR, 0.24 (CI, 0.17 to 0.34)
Metformin vs. SU	Moderate	12	SU favored for diarrhea: OR, 0.41 (CI, 0.24 to 0.72); abdominal pain: OR, 0.44 (CI, 0.29 to 0.67); nausea and vomiting: OR, 0.45 (CI, 0.31 to 0.65); and any GI adverse events: OR, 0.45 (CI, 0.28 to 0.72)
Metformin vs. DPP-4 inhibitors	High	6	DPP-4 inhibitors favored for nausea: OR, 0.37 (CI, 0.15 to 0.91), and diarrhea: OR, 0.38 (CI, 0.18 to 0.83)
Metformin vs. SGLT-2 inhibitors	Low	4	SGLT-2 inhibitors favored for diarrhea and nausea
TZD vs. SU	High	5	Neither favored; range in OR, 0.78 to 2.0; range in RD, −1.2% to 1.7%
TZD vs. DPP-4 inhibitors	Low	2	Neither favored
SU vs. DPP-4 inhibitors	Low	2	Neither favored
Metformin vs. metformin combination			
Metformin vs. metformin + TZD	Moderate	6	Metformin + TZD favored for diarrhea; OR, 0.59 (CI, 0.45 to 0.76)
Metformin vs. metformin + SU	Low	12	Neither drug favored for diarrhea or any GI adverse events
Metformin vs. metformin + DPP-4 inhibitors	Moderate	7	Neither favored; OR, 0.90 (CI, 0.63 to 1.31) for nausea; OR, 0.92 (CI, 0.68 to 1.25) for any GI adverse event; OR, 1.12 (CI, 0.64 to 1.96) for vomiting
Metformin vs. metformin + SGLT-2 inhibitors	Moderate	3	Neither favored for diarrhea; OR, 0.89 (CI, 0.54 to 1.46)
Combination vs. combination			
Metformin + TZD vs. metformin + SU	Moderate	5	Neither favored; range in OR, 0.5 to 2.0; range in RD, −5.0% to 2.1%
Metformin + TZD vs. metformin + DPP-4 inhibitors	Low	3	Neither favored
Metformin + SU vs. metformin + DPP-4 inhibitors (long-term studies)	High	4	Neither favored for diarrhea at 104 wk; OR, 0.97 (CI, 0.76 to 1.24)
Metformin + SU vs. metformin + SGLT-2 inhibitors	Low	3	Neither favored
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	Low	2	No difference
Genital mycotic infections			
Monotherapy vs. monotherapy			
Metformin vs. SGLT-2 inhibitors	Moderate	4	Metformin favored; OR, 4.1 (CI, 2.0 to 8.3)
DPP-4 inhibitors vs. SGLT-2 inhibitors	Low	2	DPP-4 inhibitors favored
Metformin vs. metformin combination			
Metformin vs. metformin + SGLT-2 inhibitors	High	9	Metformin favored; OR, 3.0 (CI, 1.2 to 7.2) for females, and OR, 2.7 (CI, 0.8 to 9.0)† for males; RD, −2.3% to 9.9%
Combination vs. combination			
Metformin + SU vs. metformin + SGLT-2 inhibitors	High	3	Metformin + SU favored; OR, 5.2 (CI, 3.4 to 8.0) for females and 7.6 (CI, 4.0 to 14.4) for males; RD 7.1% to 17.4%
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	Moderate	5	Metformin + DPP-4 inhibitors favored; RD, −2.8% to 8.8%

DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; OR = odds ratio; RD = risk difference; SGLT-2 = sodium–glucose cotransporter-2; SU = sulfonylurea; TZD = thiazolidinedione.
* Includes only estimates for comparisons with high or moderate strength of evidence.
† Effect is not statistically significant.